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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

JUL 26 1994

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: RfD/Peer Review Report of Prometryn [2,4-bis(isopropylamino)-6-(methylthio)-s-triazine].

CASRN. 7287-19-6
EPA Chem. Code: 080805
Caswell No. 097

FROM: George Z. Ghali, Ph.D.
Manager, RfD/Quality Assurance Peer Review
Health Effects Division (7509C)

7/26/94
for

TO: Robert Taylor, PM 25
Fungicide-Herbicide Branch
Registration Division (7505C)

Lois Rossi, Chief
Re-registration Branch
Special Review and Re-registration Division (7508W)

The Health Effects Division RfD/Peer Review Committee met on May 19, 1994 to discuss and evaluate the existing and recently submitted toxicology data in support of Prometryn re-registration and to re-assess the Reference Dose (RfD) for this chemical.

Material available for review included data evaluation records (DER's) for two chronic toxicity/carcinogenicity studies in rats (83-5 or 83-1a and -2a), a carcinogenicity study in mice (83-2b), a chronic toxicity study in dogs (83-1b), developmental toxicity studies in rats and rabbits (83-3a and -3b), two multi-generation reproductive toxicity studies in rats (83-4) and a subacute (28-day) toxicity study in mouse.

The Committee considered the chronic toxicity study in rats (83-1a, MRID No. 41901201) and dogs (83-1b, MRID No. 00042794) to be acceptable and the data evaluation records (HED Doc. 0010759, 001830) to be adequate. The older chronic toxicity study in rats (MRID No. 00042794) was considered to be inadequate.

The Committee considered the carcinogenicity phase of the chronic toxicity/carcinogenicity study in rats (MRID No. 41901201)

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to be acceptable and the data evaluation records (HED Doc. No. 0010759) to be adequate. The dose levels tested in the rat study were considered to be adequate for carcinogenicity testing. The carcinogenicity study in mice (MRID No. 40466201) was upgraded from Core-supplementary to Core-minimum data. The high dose levels tested in this study, though inadequate for carcinogenicity testing, were considered close to one half of the limit dose in mice. The Committee noted that there was no carcinogenic response of any type at any site in mice that might warrant repeat of the study at higher dose levels. Furthermore, all tumors observed with other members of the s-triazine class were mainly in rats and not in mice. The data evaluation record for this study (HED Doc. No. 010759) was considered to be adequate. The Committee concluded that the treatment did not alter the spontaneous tumor profile for these strains of rat and mice under the testing conditions. On this basis the chemical was classified as a "Group E".

The reproductive toxicity study in rats (83-4, MRID No. 41445101) and the developmental toxicity study in rats (83-1a, MRID No. 40457517) and rabbits (83-3b, MRID No. 00157995) were considered to be acceptable and the data evaluation records (HED Doc. No. 010759; 010759; 005665) were considered to be adequate. The Committee attributed the decreases in food consumption, body weight and body weight gain observed at the middle and high dose-levels in the reproductive toxicity study to palatability of the treated diet. The Committee recommended to combine and increase the no-observable effect levels (NOEL's) for systemic and reproductive toxicity. The reproductive/systemic NOEL should be revised from 0.6 mg/kg/day for males and 0.7 mg/kg/day for females to 47.8 and 53.6 mg/kg/day for males and females, respectively. An older reproductive toxicity study in rats (MRID No. 00024472) was available for review by the Committee and was judged to to be unacceptable since no maternal toxicity was demonstrated at the highest dose tested. There was no evidence, however, based on the available data, to suggest that prometryn was associated with significant developmental or reproductive toxicity under the testing conditions.

The RfD for this chemical was first determined by the Health Effects Division - RfD Committee on October 10, 1986, reassessed by the Health Effects Division -RfD Committee on March 17, 1987, and verified by the Agency RfD Work Group on April 15, 1987. At that time, the RfD was based on a chronic feeding study in dogs with a NOEL of 3.75 mg/kg/day, the middle dose level tested. Degenerative changes in liver and kidneys and bone marrow atrophy were observed at 37.5 mg/kg/day, the highest dose level tested. An uncertainty factor (UF) of 100 was applied to account for the inter-species extrapolation and intra-species variability. An additional UF of 10 was used to compensate for the lack of chronic and reproductive toxicty data in rats. On this basis, the RfD was calculated to be 0.004 mg/kg/day. Subsequently, chronic and reproductive toxicty studies in rats were submitted, demonstrating

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higher NOEL's than that established in the dog study which was originally used to set the RfD , i. e. the dog was the most sensitive species for the toxic effect of prometryn.

In the meeting of May 19, 1994, the Committee recommended that the basis used to establish the RfD remain unchanged. The Committee further recommended lowering the UF from 1000 to 100 since the data gaps cited above were fulfilled. On this basis, the RfD was calculated to be 0.04 mg/kg/day.

It should be noted that this chemical has not been reviewed by the World Health Organization (WHO).

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A. Individuals in Attendance

1. Peer Review Committee Members and Associates Present (Signature indicates concurrence with the peer review unless otherwise stated).

William Burnam

Reto Engler

Karl Baetcke

Henry Spencer

Roger Gardner

James Rowe

Esther Rinde

George Ghali

Rick Whiting

2. Peer Review Committee Members and Associates in absentia (Signature indicates concurrence with the peer review unless otherwise stated).

Marcia Van Gemert

William Sette

3. Scientific Reviewer (Committee or non-committee members responsible for data presentation; signatures indicate technical accuracy of panel report).

Myron Ottley

Marion Copley

3. Others:

L. Kutney and C. Frick of HED as observers.

CC: Penny Fenner-Crisp
Richard Schmitt
Kerry Dearfield
Karl Baetcke
Marion Copley
Myron Ottley
James Kariya
Flora Chow

RfD and Caswell Files

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B. Material Reviewed

Material available for review included data evaluation records for chronic toxicity/carcinogenicity studies in rats (83-5 or 83-1a and -2a), a carcinogenicity study in mice (83-2b), chronic toxicity studies in dogs (83-1b), developmental toxicity studies in rats and rabbits (83-3a and -3b), multi-generation reproductive toxicity studies in rats (83-4), and subchronic toxicity studies in rats and dogs (82-1a and -1b).

1. Chau, R. Y. et al. (1991). 104-week oral toxicity/carcinogenicity study in rats. MRID No. 41901201, HED Doc. No. 0010759. Classification: Guideline data. This study satisfies data requirement 83-1a and -2a of Subpart F of the Pesticide Assessment Guideline for chronic toxicity/carcinogenicity testing in rats.

2. Kundzins, W. (1981). 102-Week carcinogenicity study in mice: Prometryn technical. MRID No. 40466201, HED Doc. No. 010759. Classification: Core-minimum data (as upgraded by the Committee). This study satisfies data requirement 83-2b of Subpart F of the Pesticide Assessment Guideline for carcinogenicity testing in mice.

3. Woodard, M. W. et al. (1965). Prometryn safety evaluation by oral administration to rats for 104 weeks and to dogs for 106 weeks. MRID No. 00042794, HED Doc. No. 001830. Classification: Core-minimum data. This study satisfies data requirement 83-1b and of Subpart F of the Pesticide Assessment Guideline for chronic toxicity testing in dogs.

4. Giknis, M. L. A. and Yau, E. T. (1990). Prometryn technical: Two-generation reproductive toxicity study in rats. MRID No. 41445101, HED Doc. No. 010759. Classification: Core-minimum data. This study satisfies data requirement 83-4 of Subpart F of the Pesticide Assessment Guideline for reproductive toxicity testing in rats.

5. Weissenborn, J. et al. (1987). Prometryn technical: A teratology study in rats. MRID No. 40457517, HED Doc. No. 010759. Classification: Core-supplementary data (for technical and not for scientific reasons; purity information on the technical material is required). This study satisfies data requirement 83-3a of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rats.

6. Wallace, P. et al. (1985). Prometryn technical: A teratology study in New Zealand white rabbits. MRID No. 00157995, HED Doc. No. 005665. Classification: Core-minimum data. This study satisfies data requirement 83-3b of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rabbits.

END